

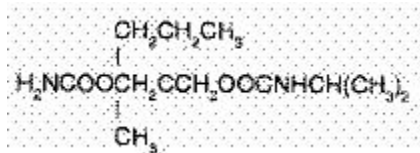
**CARISOPRODOL, ASPIRIN AND CODEINE PHOSPHATE - carisoprodol, aspirin and codeine phosphate tablet**  
Actavis Totowa LLC

**RX Only**

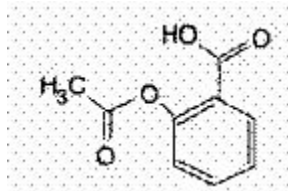
**DESCRIPTION**

Carisoprodol, Aspirin, and Codeine Phosphate Tablets is a combination product containing carisoprodol, a centrally-acting muscle relaxant, plus aspirin, an analgesic with antipyretic and antiinflammatory properties and codeine phosphate centrally-acting narcotic analgesic.

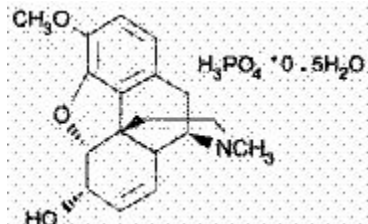
Chemically, carisoprodol is (+)-2-Methyl-2-propyl-1,3-propanediol carbamate isopropyl-carbamate. Carisoprodol is a white crystalline powder, having a mild, characteristic odor and a bitter taste. It is very slightly soluble in water, freely soluble in alcohol; in chloroform and in acetone. Its molecular formula is  $C_{12}H_{24}N_2O_4$ , with a molecular weight of 260.34. The structural formula is:



Chemically, aspirin is salicylic acid acetate. It can appear as white crystals, commonly tabular or needle-like, or white crystalline powder. It is odorless or has a faint odor. It is slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether; sparingly soluble in absolute ether. Its molecular formula is  $C_9H_8O_4$  with a molecular weight of 180.16. The structural formula is:



Chemically, codeine phosphate appears as fine, odorless, white needle-shaped crystals, or white crystalline powder. Is affected by light. Its solutions are acid to litmus. Freely soluble in water; very soluble in hot water at 80°; slightly soluble in alcohol but more so in boiling alcohol. Its molecular formula  $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot 1/2 H_2O$ , with a molecular weight of 406.37. The structural formula is:



Each tablet, for oral administration, contains 200 mg of carisoprodol, 325 mg of aspirin and 16 mg codeine phosphate. In addition, each tablet contains the following inactive ingredients: D&C Yellow #10 aluminum lake, corn starch, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, silicon dioxide, sodium starch glycolate, stearic acid, and zinc stearate.

**CLINICAL PHARMACOLOGY**

**Carisoprodol:** Carisoprodol is a centrally acting muscle relaxant that does not directly relax tense skeletal muscles in man. The mode of action of Carisoprodol in relieving acute muscle spasm of local origin has not been clearly identified, but may be related to its sedative properties. In animals, carisoprodol has been shown produce muscle relaxation by blocking interneuronal activity and depressing transmission of polysynaptic neurons in spinal cord and in the descending reticular formation of the brain. The onset of action is rapid and lasts four to six hours.

Carisoprodol is metabolized in the liver and is excreted by the kidneys. It is dialyzable by peritoneal and hemodialysis.

**Aspirin:** Aspirin is a nonnarcotic analgesic with antiinflammatory and antipyretic activity. Inhibition of prostaglandin biosynthesis appears to account for most of its antiinflammatory and for at least part of its analgesic and antipyretic properties.

Aspirin is rapidly absorbed and almost totally hydrolyzed to salicylic acid following oral administration. Although aspirin has a half-life of only about 15 minutes, the apparent biologic half-life of salicylic acid in the therapeutic plasma concentration range is between 6 and 12 hours. Salicylic acid is eliminated by renal excretion and by biotransformation to inactive metabolite. Clearance of salicylic acid in the high-dose range is sensitive to urinary pH (see Drug Interactions) and is reduced by renal dysfunction.

**Codeine Phosphate:** Codeine phosphate is a centrally acting narcotic-analgesic. Its actions are qualitatively similar to morphine, but its potency is substantially less.

Clinical studies have shown combining aspirin and codeine produces a significant additive effect in analgesic efficacy.

## INDICATIONS AND USAGE

Carisoprodol, Aspirin and Codeine Phosphate Tablets are indicated as an adjunct to rest physical therapy, and other measures for the relief of pain, muscle spasm, and limited mobility associated with acute, painful musculoskeletal conditions when the additional actions of codeine is desired.

## CONTRAINDICATIONS

Acute intermittent porphyria; bleeding disorders; allergic or idiosyncratic reactions to carisoprodol, aspirin, codeine, or related compounds.

## WARNINGS

On very rare occasions, the first dose of Carisoprodol has been followed by idiosyncratic reactions with symptoms appearing within minutes or hours. These may include extreme weakness, transient quadriplegia, dizziness, ataxia temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion and disorientation. Although symptoms usually subside over the course of the next several hours, discontinue Carisoprodol, Aspirin and Codeine Phosphate Tablets and initiate appropriate supportive and symptomatic therapy, which may include epinephrine and/or antihistamines. In severe cases, corticosteroids may be necessary. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock.

The effects of carisoprodol with agents such as alcohol, other CNS depressants or psychotropic drugs may be additive. Appropriate caution should be exercised with patients who take one or more of these agents simultaneously with Carisoprodol, Aspirin and Codeine Phosphate tablets.

## PRECAUTIONS

### General

To avoid excessive accumulation of carisoprodol, aspirin or their metabolites, use Carisoprodol, Aspirin and Codeine Phosphate tablets with caution in patients with compromised liver or kidney function, or in elderly or debilitated patients (see CLINICAL PHARMACOLOGY).

Use with caution in patients with history of gastritis or peptic ulcer, in patients on anticoagulant therapy, and in addiction-prone individuals.

### *Ultra-rapid Metabolizers of Codeine:*

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6\*2X2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1-10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians and Arabs. Data is not available for other ethnic groups.

When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and should inform their patients about these risks and the signs of morphine overdose. (See PRECAUTIONS – Nursing Mothers)

### Information for Patients

Caution patients that some people have a variation in a liver enzyme and change codeine into morphine more rapidly and completely than other people. These people are ultra-rapid metabolizers and are more likely to have higher-than-normal levels of morphine in their blood after taking codeine which can result in overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. In most cases, it is unknown if someone is an ultra-rapid codeine metabolizer.

Nursing mothers taking codeine can also have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies. Instruct nursing mothers to watch for signs of morphine toxicity in their infants including increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Instruct nursing mothers to talk to the baby's doctor immediately if they notice these signs and, if they cannot reach the doctor right away, to take the baby to an emergency room or call 911 (or local emergency services).

### Nursing Mother

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. Despite the common use of codeine products to manage postpartum pain, reports of adverse events in infants are rare. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

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The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding. (See PRECAUTIONS—General—Ultra-rapid Metabolizers of Codeine)

#### Information for Patients:

Caution patients that this drug may impair the mental and /or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Caution patients with a predisposition for gastrointestinal bleeding that concomitant use of aspirin and alcohol may have additive effect in this regard.

Caution patients that dosage of medications used for gout, arthritis, or diabetes may have to be adjusted when aspirin is administered or discontinued (see Drug interactions).

#### Drug Interactions

Clinically important interactions may occur when certain drugs are administered concomitantly with aspirin or aspirin-containing drugs.

1. Oral Anticoagulants-By interfering with platelet function or decreasing plasma prothrombin concentration, aspirin enhances the potential for bleeding in patients on anticoagulants.
2. Methotrexate-aspirin enhances the toxic effects of this drug.
3. Probenicid and Sulfipyrazone-large doses of aspirin reduce the uricosuric effect of both drugs. Renal excretion of salicylate may also be reduced.
4. Oral Antidiabetic Drugs-enhancement of hypoglycemia may occur.
5. Antacids-to the extent that they raise urinary pH, antacids may substantially decrease plasma salicylate concentrations; conversely, their withdrawal can result in a substantial increase.
6. Ammonium Chloride-this and other drugs that acidify a relatively alkaline urine can elevate plasma salicylate concentrations.
7. Ethyl Alcohol-enhanced aspirin -induced fecal blood loss has been reported.
8. Corticosteroids-salicylate plasma levels may be decreased when adrenal corticosteroids are given, and may be increased substantially when they are discontinued.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been done with Carisoprodol, Aspirin and Codeine Phosphate Tablets.

#### Pregnancy

##### Teratogenic Effects

**Pregnancy Category C.** Adequate animal reproduction studies have not been conducted with Carisoprodol, Aspirin and Codeine Phosphate Tablets. It is also not known whether Carisoprodol, Aspirin and Codeine Phosphate Tablets can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Carisoprodol, Aspirin and Codeine Phosphate Tablets should be given to a pregnant woman only if clearly needed.

Studies in rodents have shown salicylates to be teratogenic when given in early gestation, and embryocidal when given in later gestation in doses considerably greater than usual therapeutic doses in humans. Studies in women who took aspirin during pregnancy have not demonstrated an increased incidence of congenital abnormalities in the offspring.

## **Labor and Delivery**

Ingestion of aspirin near term or prior to delivery may prolong delivery or lead to bleeding in mother, fetus, or neonate.

## **Nursing Mothers**

Carisoprodol is excreted in human milk in concentrations two-to-four times that in maternal plasma. Aspirin is excreted in human milk in moderate amounts and can produce a bleeding tendency in nursing infants. Because of the potential for serious adverse reaction in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

## **Pediatric Use**

Safety and effectiveness in pediatric patients below the age of twelve have not been established.

## **ADVERSE REACTIONS**

If severe reactions occur, discontinue Carisoprodol, Aspirin and Codeine Phosphate Tablets and initiate appropriate symptomatic and supportive therapy.

The following side effects which have occurred with the administration of the individual ingredients alone may also occur with the combination.

**Carisoprodol:** Central Nervous System-Drowsiness is the most frequent complaint and along with other CNS effects may require dosage reduction. Observed less frequently are dizziness, vertigo and ataxia. Tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia have been infrequent or rare.

**Idiosyncratic** - Idiosyncratic reactions are very rare. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug (see WARNINGS).

**Allergic** - Skin rash, erythema multiforme, pruritis, eosinophilia, and fixed drug eruptions with cross-reaction to meprobamate have been reported. If allergic reactions occur, discontinue Carisoprodol, Aspirin and Codeine Phosphate Tablets and treat symptomatically. In evaluating possible allergic reactions, also consider allergy to excipients (information on excipients is available to physicians on request).

**Cardiovascular** - Tachycardia, postural hypotension, and facial flushing.

**Gastrointestinal** - Nausea, vomiting, epigastric distress, and hiccup.

**Hematologic** - No serious blood dyscrasias have been attributed to carisoprodol alone. Leukopenia and pancytopenia have been reported, very rarely, in situations in which other drugs or viral infections may have been responsible.

**Aspirin:** The most common adverse reactions associated with the use of aspirin have been gastrointestinal, including nausea, vomiting, gastritis, occult bleeding, constipation, and diarrhea. Gastric erosion, angioedema, asthma, rash, pruritus and urticaria have been reported less commonly. Tinnitus is a sign of high serum salicylate levels (see OVERDOSAGE).

**Aspirin Intolerance** - Allergic type reactions in aspirin-sensitive individuals may involve the respiratory tract or the skin. Symptoms of the former, range from rhinorrhea and shortness of breath to severe asthma and the latter may consist of urticaria, edema, rash, or angioedema (giant hives). These may occur independently or in combination.

**Codeine Phosphate:** Nausea, vomiting, constipation, miosis, sedation, and dizziness have been reported.

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance**

Schedule CIII (see PRECAUTIONS).

### **Abuse**

In clinical use, has been rare.

### **Dependence**

In clinical use, dependence with Carisoprodol, Aspirin, and Codeine Tablets has been rare and there have been no reports of significant abstinence signs. Nevertheless, the following information on the individual ingredients should be kept in mind.

**Carisoprodol** - In dogs, no withdrawal symptoms occurred after abrupt cessation of carisoprodol from dosages as high as 1 gm/kg/day. In a study of man, abrupt cessation of 100 mg/kg/day (about five times the recommended daily adult dosage) was followed in some subjects by mild withdrawal symptoms such as abdominal cramps, insomnia, chills, headache, and nausea. Delirium and convulsions did not occur (see PRECAUTIONS).

Codeine Phosphate Drug dependence of the morphine type may result.

## **OVERDOSAGE**

**Signs and symptoms:** Any of the following which have been reported with the individual ingredients may occur and may be modified to a varying degree by the effects of the ingredients present in Carisoprodol, Aspirin and Codeine Phosphate Tablets.

**Carisoprodol** - Stupor, coma, shock, respiratory depression, and, very rarely, death. Overdosage with carisoprodol in combination with alcohol, other CNS depressants, or psychotropic agents can have additive effects, even when one of the agents has been taken in the usually recommended dosage.

*Aspirin* - Headache, tinnitus, hearing difficulty, dim vision, dizziness, lassitude, hyperpnea, rapid breathing, thirst, nausea, vomiting, sweating, and occasionally diarrhea are characteristic of mild to moderate salicylate poisoning. Salicylate poisoning should be considered in children with symptoms of vomiting, hyperpnea, and hyperthermia.

Hyperpnea is an early sign of salicylate poisoning, but dyspnea supervenes at plasma levels above 50 mg/dL. These respiratory changes eventually lead to serious acid-base disturbances. Metabolic acidosis is a constant finding in infants but occurs in older children only with severe poisoning; adults usually exhibit respiratory alkalosis initially and acidosis terminally.

Other symptoms of severe salicylate poisoning include hyperthermia, dehydration, delirium, and mental disturbances. Skin eruptions, GI hemorrhage, or pulmonary edema are less common. Early CNS stimulation is replaced by increasing depression, stupor, and coma. Death is usually due to respiratory failure or cardiovascular collapse.

*Codeine Phosphate* - pinpoint pupils, CNS depression, coma, respiratory depression, and shock.

**Treatment:**

*General* - Provide symptomatic and supportive treatment, as indicated. Any drug remaining in the stomach should be removed using appropriate procedures and caution to protect the airway and prevent aspiration, especially in the stuporous or comatose patient. Incomplete gastric emptying with delayed absorption of carisoprodol has been reported as a cause for relapse. Should respiration or blood pressure become compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously, as indicated.

*Carisoprodol* - The following have been used successfully in overdosage with the related drug meprobamate: diuretics, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis (see CLINICAL PHARMACOLOGY). Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Carisoprodol can be measured in biological fluid by gas chromatography (Douglas, j.f., et al: J Pharm Sci 58:145,1969).

*Aspirin* - Since there are no specific antidotes for salicylate poisoning, the aim of treatment is to enhance elimination of salicylate and prevent or reduce further absorption; to correct any fluid electrolyte or metabolic imbalance; and to provide general and cardiorespiratory support. If acidosis is present, intravenous sodium bicarbonate must be given, along with adequate hydration, until salicylic levels decrease to within the therapeutic range. To enhance elimination, forced diuresis and alkalinization of urine may be beneficial. The need for hemoperfusion or hemodialysis is rare and should be used only when other measures have failed.

*Codeine Phosphate* - Narcotic antagonists, such as nalorphine and levallorphan, may be indicated.

**DOSAGE AND ADMINISTRATION**

**Usual Adult dosage;** 1 or 2 tablets, four times daily. Not recommended for use in children under age twelve.

**HOW SUPPLIED**

Carisoprodol, Aspirin and Codeine Phosphate tablets (carisoprodol 200 mg, aspirin 325 mg, and codeine phosphate, 16 mg) are yellow and white color, two-layered round unscored tablets, debossed 'A 138' on one side. The tablets are available in bottles of 100 and 500. Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight container.

Manufactured by: Actavis Totowa LLC  
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